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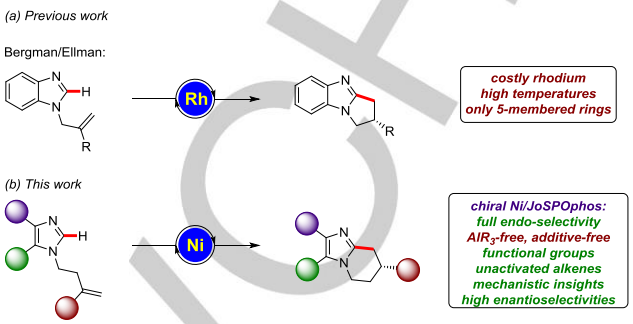
Enantioselective Aluminum-Free Alkene Hydroarylations *via* C–H Activation by a Chiral Nickel/JoSPOphos Manifold

Joachim Loup,[+] Valentin Müller,[+] Debasish Ghorai, and Lutz Ackermann*

Abstract: Highly enantioselective nickel-catalyzed alkene *endo*-hydroarylations were accomplished with full selectivity *via* organometallic C–H activation. The asymmetric assembly of chiral six-membered scaffolds proved viable in the absence of pyrophoric organoaluminum reagents within an unprecedented nickel/JoSPOphos manifold.

The selective modification of omnipresent C–H bonds has been recognized as a transformative tool in molecular syntheses.[1] While major progress was realized with the aid of noble 4d and 5d transition metals, recent focus has shifted towards Earth-abundant and less toxic 3d metals.[2] Despite significant advances in organometallic catalysis, full selectivity control towards enantioselective C–H functionalizations continues to heavily rely on precious 4d transition metals, prominently featuring palladium and rhodium complexes.[3] In sharp contrast, enantioselective C–H activations with inexpensive 3d base metals continue to be scarce.[4] Based on the elegant studies by Bergman and Ellman, undirected cyclizations of azoles have been dominated by rhodium(I) catalysts,[5] with a single enantioselective transformation being reported thus far.[6] In recent years, nickel-catalyzed[7] cyclizations *via* C–H activation[8] have emerged as a viable tool for molecular syntheses, predominantly delivering the *exo*-products.[8a,8c-e] However, enantioselective *endo*-cyclizations *via* C–H activation have proven elusive, with a notable exception featuring pyridones.[8b,8c] Despite major progress, this approach was limited to strongly activated azolium salts,[8e] and/or pyrophoric organoaluminum reagents as Lewis-acidic additives. In contrast, within our program on nickel-catalysis[9] with secondary phosphine oxide (SPO) pre-ligands,[10] we have devised the unprecedented nickel-catalyzed enantioselective *endo*-cyclization of imidazoles with alkenes. Notable features of our strategy include 1) the use of Earth-abundant nickel catalysts for synthetically meaningful alkene hydroarylation, 2) asymmetric secondary C–H alkylations of biologically relevant (benz)imidazoles[11] and purines,[12] 3) first nickel-catalyzed *endo*-selective cyclizations of azoles, 4) unactivated alkenes, 5) organoaluminum-free conditions with unmatched functional group tolerance, and 6) detailed mechanistic insights on a novel nickel/JoSPOphos design (Scheme 1).



Scheme 1. Asymmetric hydroarylations *via* nickel-catalyzed C–H activation.

We initiated our studies by testing a wealth of chiral ligands for the envisioned asymmetric alkene hydroarylation (Table 1 and Table S-1).[13] The desired product was obtained with moderate performance using preligand **L1**.[4e] Monodentate phosphoramidite **L2** provided product **2a** with poor yield and enantio-induction. In contrast, the prototypical secondary phosphine oxide (SPO)[14] **L3** led to ligand acceleration, but poor enantioselectivity. We, thus, probed further HASPO preligands, with derivative **L4** furnishing promising results. Unfortunately, all (pre)ligands required the pyrophoric $AlMe_3$ as additive. Thereafter, we tested JoSPOphos-type ligands due to their documented efficacy in rhodium(I)-catalyzed asymmetric hydrofunctionalization reactions.[15] To our delight, JoSPOphos **L9** afforded the desired product **2a** in excellent yield and enantioselectivity, while the related ligand **L10** gave moderate enantioselectivity. It is noteworthy that this transformation represents a proof of concept in that it constitutes the first use of a JoSPOphos ligand with a transition metal other than rhodium(I). Poor results were obtained with the corresponding JosiPhos phosphine ligand **L11**, highlighting the superiority of the phosphine oxide moiety. Interestingly, the C–H activation efficiently occurred with catalyst loadings as low as 1.0 mol % (entries 1 and 2), while the JoSPOphos-enabled hydroarylation proceeded even in the absence pyrophoric $AlMe_3$ (entries 3-5). Given the prospect for functional group tolerance, we further focused on the $AlMe_3$-free conditions (Table S-2).[13] Here, variations of the ligand-to-metal ratio improved the enantioselectivity slightly (entries 6-9), with an excess of the ligand **L9** providing inferior results, which is likely due to the formation of less selective bis-ligated nickel species (entries 6 and 7).

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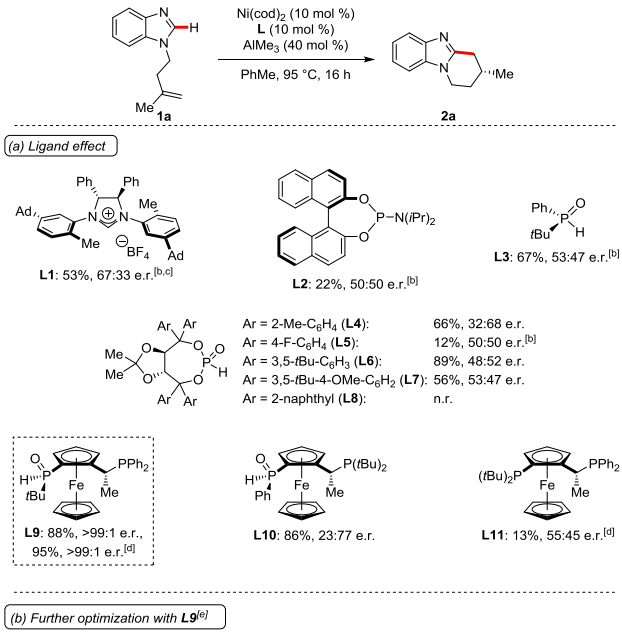
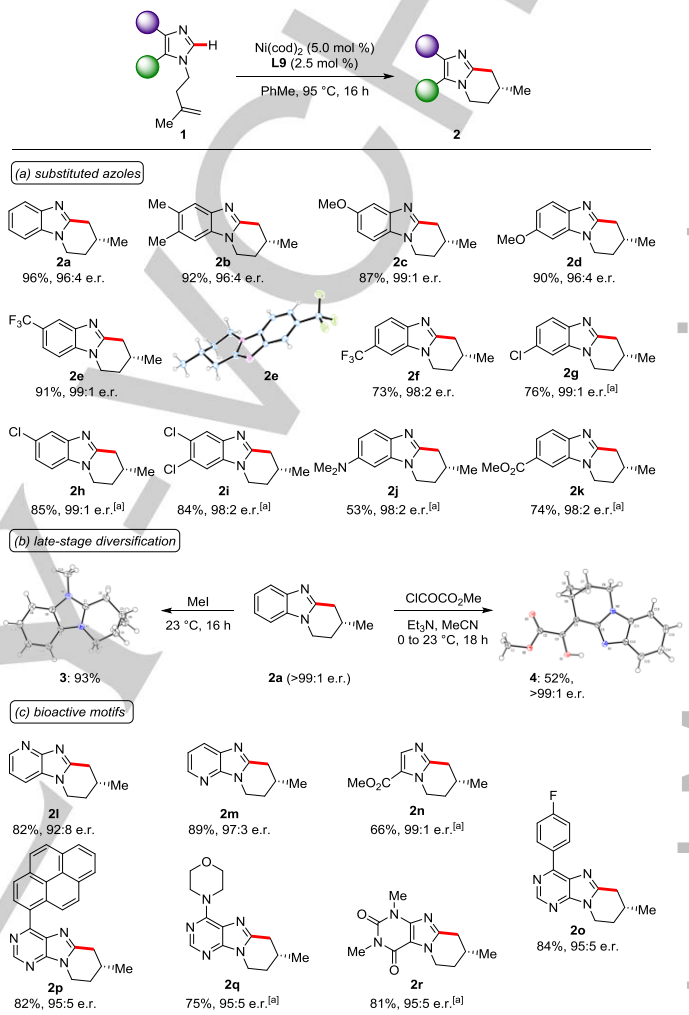
Table 1. Optimization of the enantioselective C–H alkylations.[a]



Entry	[Ni(cod)$_2$]/ mol %	[**L9**]/ mol %	[AlMe$_3$]/ mol %	Yield/%	e.r.
1	2.5	2.5	10	95	>99:1
2	**1.0**	**1.0**	**4.0**	**97**	**>99:1**
3	10	10	-	91	97:3
4	10	-	-	n.r.	-
5	-	10	-	n.r.	-
6	**5.0**	**5.0**	**-**	**98**	**89:11**
7	5.0	10	-	38	77:23
8	**5.0**	**2.5**	**-**	**96**	**96:4**
9	5.0	1.25	-	31	94:6

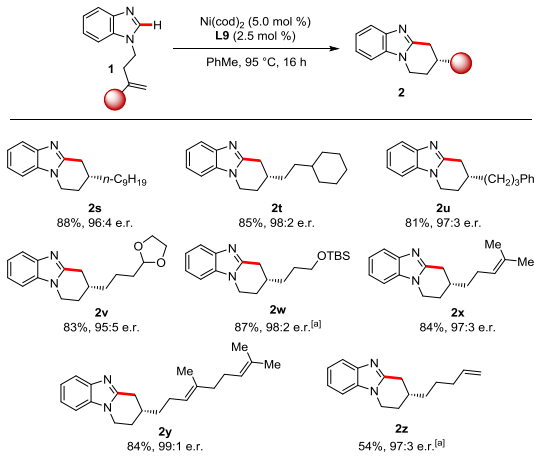
[a] Reaction conditions: **1a** (0.50 mmol), Ni(cod)$_2$ (10 mol %), **L** (10 mol %), AlMe$_3$ (40 mol %), PhMe (2.0 mL), 95 °C, 16 h. Isolated yields. Enantioselectivities determined by chiral HPLC. [b] At 130 °C. [c] NaO*t*Bu (20 mol %) was added. [d] Using Ni(cod)$_2$ (2.5 mol %), **L9** (2.5 mol %) and AlMe$_3$ (10 mol %) in PhMe (1.0 mL). [e] In PhMe (1.0 mL). n.r. = no reaction.

With the optimized reaction conditions in hand, we next studied the versatility of the asymmetric C–H transformation. The desired products **2** were obtained with high levels of enantiocontrol. Various substituted benzimidazoles **1** were thus identified as viable substrates (Scheme 2a).[16] The absolute configurations of product **2e** as well as the products of late-stage modification **3** and **4** were unambiguously assigned by X-ray diffraction analysis (Scheme 2b).[17] The scope of the enantioselective C–H alkylation was not limited to benzimidazoles. Indeed, imidazole **1n** and a variety of pharmaceutically relevant heterocycles, including bioactive purines and theophylline motifs **1**, were efficiently converted with high selectivity control (Scheme 2c). Thereby, biologically relevant morpholines and pyrene fluorophores proved to be compatible within the nickel/SPO regime. The AlMe$_3$-free reaction conditions translated into sensitive functional groups, such as amino, chloro and ester, being fully tolerated.



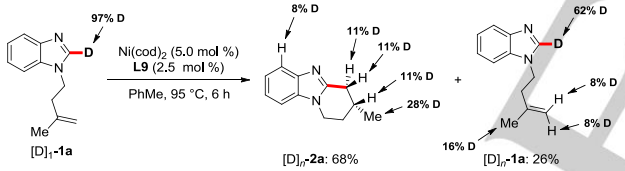
Scheme 2. Enantioselective C–H alkylations with alkenes and late-stage diversification. [a] With Ni(cod)$_2$ (10 mol %) and **L9** (5.0 mol %).

Moreover, a variety of highly functionalized tethered prochiral alkenes **1** was well accepted, providing the desired products **2** in high yields and excellent levels of enantiocontrol (Scheme 3).[13] Additional double bonds in the tethered alkene were fully accommodated, with the distal olefins remaining entirely untouched, as exemplified with *N*-γ-geranyl- **1x**, *N*-γ-farnesyl-benzimidazole **1y** and **1z**.



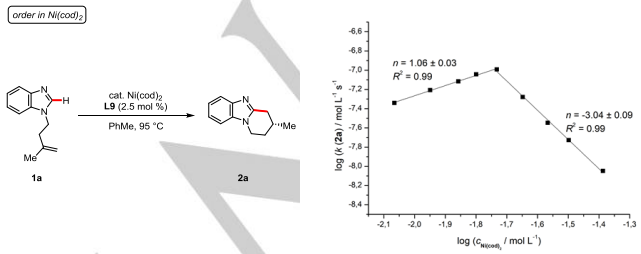
Scheme 3. Enantioselective C–H alkylations of substituted alkenes. [a] With $Ni(cod)_2$ (10 mol %) and **L9** (5.0 mol %).

Given the unique features of the asymmetric aluminum-free nickel-catalyzed C–H alkylation, we became attracted to unravel its mode of action. To this end, C–H activations with deuterium-labeled benzimidazole $[D]_1$-**1a** revealed H/D scrambling at the methyl group and positions of the original olefin (Scheme 4). This observation can be rationalized with a facile C–H scission step. Furthermore, C–H activation performed with isotopically labeled compound $[D]_1$-**1a** showed a kinetic isotope effect (KIE) of $k_H/k_D \approx 1.1$.[13]



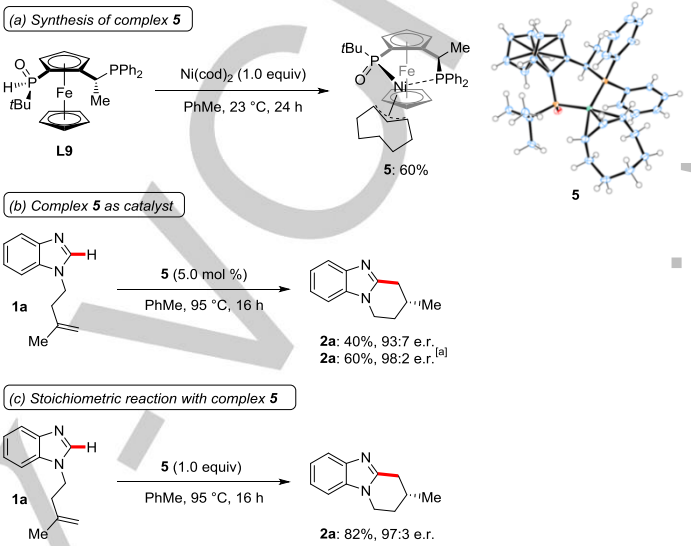
Scheme 4. Reaction with isotopically labeled substrate $[D]_1$-**1a**.

Subsequently, detailed kinetic studies of the enantioselective C–H alkylation unraveled a first-order dependence on the concentration of the substrate **1a**, the ligand **L9** and the nickel precursor (Scheme 5), in the latter case with an inhibition at higher nickel concentrations.[13] Further, the addition of free cyclooctadiene (cod) resulted in a deceleration of catalysis.[13,18]



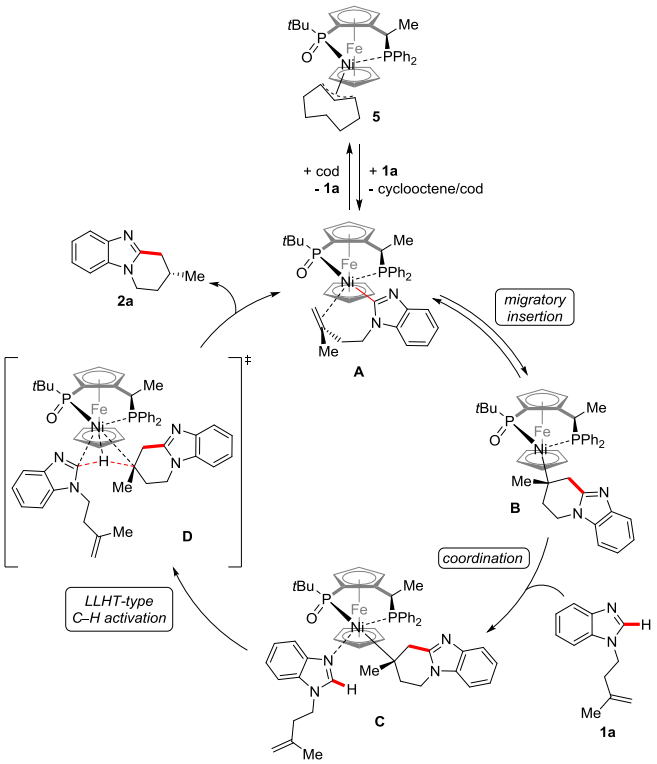
Scheme 5. Kinetic analysis of the nickel-catalyzed C−H activation.

Next, we independently prepared the novel well-defined organometallic nickel(II)-JoSPOphos complex **5** from $Ni(cod)_2$ and preligand **L9**, which was unambiguously characterized by X-ray crystallographic diffraction analysis (Scheme 6a).[17] Complex **5** was shown to be competent in both stoichiometric and catalytic settings (Scheme 6b,c). Finally, the absence of a non-linear effect (NLE) was indicative of a mono-ligated nickel catalyst being operative in the enantioselective C–H alkylation.[13,19]



Scheme 6. Synthesis and use of complex **5**. [a] With $Ni(cod)_2$ (5.0 mol %).

Based on our mechanistic studies,[20] we propose the asymmetric C–H alkylation to be initiated by the formation of the nickel(II) complex **5** (Scheme 7), which is then coordinated by substrate **1** to form the active catalyst **A**. Intermediate **A** next undergoes a fast migratory insertion to deliver the cyclized compound **B**. After a kinetically relevant coordination of a second molecule **1a** (**C**), being reflected in its first order kinetics, a facile C–H activation event takes place, which is proposed to occur by a ligand-to-ligand hydrogen transfer (LLHT) manifold (**D**).[20a,21] The observed H/D scrambling (Scheme 4) is likely due to off-cycle π-allyl nickel intermediates.



Scheme 7. Plausible catalytic cycle.

In conclusion, we have reported on the first nickel-catalyzed enantioselective *endo*-alkene-hydroarylation *via* organometallic aluminum-free C–H activation. Thus, a novel nickel/JoSPOphos manifold enabled C–H activation with high efficacy and outstanding levels of enantiocontrol. The Earth-abundant nickel catalysis did not require pyrophoric organoaluminum additives, and detailed mechanistic studies provided strong support for a facile LLHT C–H activation with first order kinetics.

Acknowledgements

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Keywords: asymmetric catalysis • nickel • C−H activation • SPOs • aluminum-free

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[16] 5-Membered rings could be formed with high levels of enantio-control as well, yet lower conversions were observed here (Table S-3 in the Supporting Information). Substrates **1** bearing aryl substituents gave thus far less satisfactory results.

[17] CCDC 1871583, 1871584, 1871585 and 1871582 for compounds **2e**, **3**, **4** and **5**, respectively, contain the supplementary crystallographic data for this contribution. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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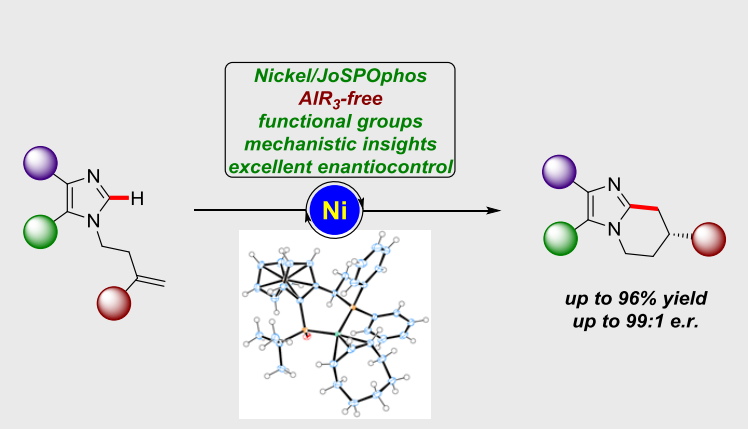

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Enantioselective Aluminum-Free Alkene Hydroarylations *via* C–H Activation by a Chiral Nickel/JoSPOphos Manifold

SPO rules: A chiral Ni/SPO regime enabled outstanding levels of enantio-control in asymmetric C–H alkylations with unactivated alkenes.